Isopropanol–Water Granulating Solution Ratio Effect on Physical Tablet Parameters

By LEONARD L. KAPLAN

A chewable multivitamin tablet formulation containing dry malt solids as binder was used as the model in this study to determine the effect of varying the ratio of isopropanol–water granulating solution on hardness, thickness, and disintegration parameters of tablets. Tablet granulations were prepared using (*a*) water, (*b*) isopropanol 25 per cent–water 75 per cent, (*c*) isopropanol 50 per cent–water 50 per cent, (*d*) isopropanol 75 per cent–water 25 per cent, and (*e*) isopropanol. Granulations (*a*) through (*d*) were compressed at a target hardness of 5 to 6 Kg. and a tablet weight of 650 mg. on the Stokes model F single-punch machine. Quantitative determinations of the physical tablet parameters were made initially following the controlled compression, and at selected storage time intervals. Granule size distribution evaluation showed an empirical relationship between solution ratios and granule size distribution as the determinant of differences in tablet thickness. Statistical analysis of the model initial and storage data revealed no significant effects on tablet hardness and disintegration.

THE PURPOSE of this report is to relate the effect of selected volume to volume ratios of isopropanol–water granulating solutions on the subsequent physical properties of a chewable multivitamin tablet formulation[1] containing dry malt solids as the binder. Underlying this objective is the determinant of a satisfactory minimal quantity of water sufficient for the granulation process so as to produce granules suitable for tableting the model formulation with prescribed chewable characteristics, utilizing isopropanol as the distributant co-solvent.

Pertinent references in the recent pharmaceutical literature concerned with granulating procedures have, for the most part, discussed the evaluation of granulating agents and methods (1, 2), the evaluation of new equipment (3), and the measurement of the physical properties of the produced compressed tablets (4). The thrust of this study is to relate the influence of the selected isopropanol–water granulating solutions on the granulations formed, and on the physical properties of the resultant compressed tablets intended to be chewed. In designing this formulation, it was recognized that dry malt solids[2] assumes an adhesive property when wetted with water, and is insoluble and nonadhesive in isopropanol. This adhesive nature of dry malt solids favored its use as the binder in this formulation. It was known that it could be added to the primary blend as a dry powder, and subsequently would form granules of a compressible character when granulated with water. Furthermore, it was known that the resultant tablets would be easy to chew without adhering to the teeth. It was decided to investigate the use of isopropanol in combination with water as the granulating solution in order to determine the minimal quantity of water to achieve granules suitable for tableting and to ensure adequate distribution of the water-wetted binder throughout the multivitamin powder blend.

EXPERIMENTAL

Formulation—The model formulation for a 1000-tablet batch quantity consisted of a primary blend of thiamine mononitrate 1.2 Gm., riboflavin 2.2 Gm., calcium pantothenate 1.5 Gm., pyridoxine HCl 0.6 Gm., niacinamide 11 Gm., ascorbic acid 33 Gm., dry malt solids 25 Gm., and diluent fillers and flavors *q.s. ad.* 600 Gm. Following the granulating procedures, vitamin A–D dry (500,000 units, 50,000 units per Gm.) 10 Gm., vitamin B_{12} (1:100) 1.5 Gm., tartaric acid 5.0 Gm., magnesium stearate 5.0 Gm., and cornstarch *q.s.* were added to the granules, yielding a total batch weight for compression of 650 Gm.

Granulating Procedures—One hundred milliliters of granulating solutions was prepared of each of the following: (*a*) water, (*b*) isopropanol 25%–water 75% v/v, (*c*) isopropanol 50%–water 50%, (*d*) isopropanol 75%–water 25%, and (*e*) isopropanol.

Five batches of the primary multivitamin blend were prepared and granulated with each of the five granulating solutions in a Hobart[3]-type 4-qt. mixer set at number two speed control. The resultant agglomerated masses were spread on trays at a 0.5-in. thickness, and dried at 100°F. to a moisture content of no more than 1% as determined on the Cenco moisture balance. Following the drying process, the dried materials were reduced to granules by passing through the model D Fitzpatrick comminutor, number two screen, slow speed, knives forward. Granulations (*a*), (*b*), (*c*), and (*d*) were satisfactory for further processing and were so submitted. Granulation (*e*) prepared with isopropanol resulted in an amorphous, nonflowing powder, and was rejected as unsuitable for normal tableting procedures.

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[1] Marketed as Viacets by Walker Laboratories, Division of Richardson-Merrell, Inc., Mount Vernon, N.Y.

[2] A mixture of soluble dextrins and malt sugars obtained from barley.

[3] Hobart Manufacturing Co., Troy, Ohio.

Granule Analyses—A granule size distribution study was conducted on each of the four primary blend granulations (*a*) through (*d*), utilizing the Cenco-Meinzer sieve shaker. The results of this analysis are shown in Table I expressed as the percentage retained on screen mesh sizes 0–16, 16–24, 24–30, 30–40, 40–60, and the residual passing through the 60-mesh screen as fines. These residual quantities are plotted against the percentage of water in the granulating solutions as shown in Fig. 1. The resultant negative, straight-line slope suggests an inverse linear relationship between the ratio of water in the granulating solution and the percentage of residual fines in the granulation.

The granule distribution data are presented in Table II on a percentage cumulative retention basis on mesh screens 16, 24, 30, 40, and 60. The plot of these data against the percentage of water in the granulating solutions is shown in Fig. 2. These slopes reveal an increasing degree of influence of the proportion of water in the granulating solutions on the per cent granules retained cumulatively on the 40- and the 60-mesh screens. The per cent granules retained on the 16-, 24-, and 30-mesh screens does not reveal an appreciably consistent pattern of increased retention with the increased granulating solution water ratios.

Tableting Procedures—Following the addition of the balance of the formula ingredients and subsequent mixing in a twin-shell type blender for 20 min. to ensure uniform dispersion of all ingredients, each of the four granulations (*a*), (*b*), (*c*), and (*d*) was compressed on the Stokes model F single-punch tablet machine, using 0.5-in. standard concave punches.

The target tablet weight was 650 mg., and the target hardness was 5 to 6 Kg. hardness, as measured with the Stokes tablet hardness tester. The thickness of the tablet thus became a variable dependent on the compression characteristics of each of the granulations. In a previously published article (5), the author studied the compression characteristics of pharmaceutical materials, *per se*. It was reported that the thickness of compressed materials varied with the volumetric fill weight of the die cavity, which in turn appeared to be a function of the density of the material subjected to compression. Following the compression of each of the four granulations (*a*), (*b*), (*c*), and (*d*), the weight, hardness, thickness, and disintegration of the tablets were determined. These results are shown in Table III.

Figure 3 represents the plots of the per cent granules cumulatively retained on the 60-mesh screen and the thickness of the compressed tablets prepared with each of the four granulations. The resultant slope is empirically suggestive of an inverse relationship between these two variables.

Friability tests were conducted, utilizing the Roche Friabilator apparatus. In this procedure, 20

TABLE I—GRANULE DISTRIBUTION

Mesh Sizes[a]	Granulations (*a*)	(*b*)	(*c*)	(*d*)
Retained on 16	5.2	2.3	2.7	1.8
Through 16, on 24	12.8	12.3	12.8	10.6
Through 24, on 30	8.2	6.0	5.2	3.9
Through 30, on 40	20.0	17.2	13.1	9.0
Through 40, on 60	14.8	14.2	9.6	8.0
Residual through 60	39.0	48.0	56.6	66.7
	100.0%	100.0%	100.0%	100.0%

[a] U.S. Standard sieve series, Newark Wire Cloth Co., Newark, N.J.

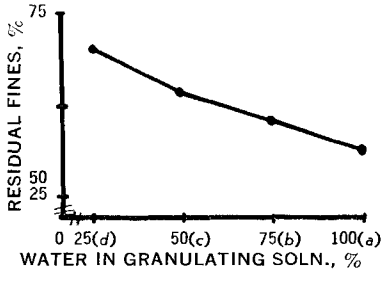

Fig. 1—Residual fines through No. 60-mesh screen.

TABLE II—GRANULE CUMULATIVE RETENTION (EXPRESSED IN PER CENT)

Granulations	Mesh Sizes 16	24	30	40	60
(*a*)	5.2	18.0	26.2	46.2	61.0
(*b*)	2.3	14.6	20.6	37.8	52.0
(*c*)	2.7	15.5	20.7	33.8	43.7
(*d*)	1.8	12.4	16.3	25.3	33.3

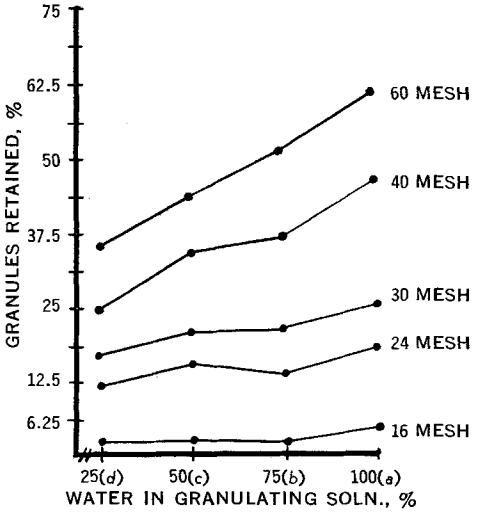

Fig. 2—Cumulative granule retention on selected mesh sizes.

TABLE III—PHYSICAL TABLET PROPERTIES

Granulations	Wt.,[a] mg.	Hardness,[a] Kg.	Thickness,[a] in.	Disintegration,[b] min.
(*a*)	647	5.1	.209	8
(*b*)	653	5.3	.214	7
(*c*)	662	5.5	.217	10
(*d*)	659	5.5	.219	12

[a] Means of 15 determinations. [b] Means of 6 determinations, U.S.P. tablet disintegration apparatus, water, without disks.

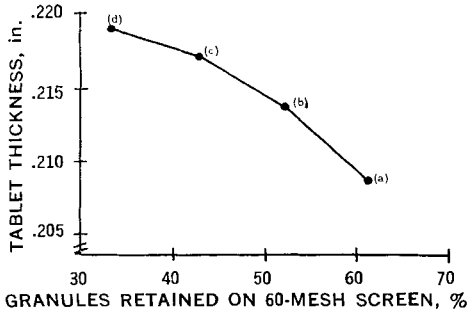

Fig. 3—Relationship of granules cumulatively retained and the resultant tablet thickness of the four test granulations (a) *through* (d).

TABLE IV—FRIABILITY STUDY DATA

Formula	3 min. Wt. Loss,[a] mg.	6 min. Wt. Loss,[a] mg.	9 min. Wt. Loss,[a] mg.
(*a*)	2	6	8
(*b*)	4	7	9
(*c*)	3	6	8
(*d*)	3	6	9

[a] Average loss of 20 tablets.

tablets of each of the four granulations were placed in the apparatus, and the apparatus rotated at 24 r.p.m. for periods of 3 min., 6 min., and 9 min. in order to introduce a time dimension in the evaluation of the relative friability of the four tablet formulations. The results obtained in terms of average tablet weight loss are presented in Table IV. No significant differences were noted among the four formulations.

Storage Data—Following storage for 4 months at ambient room temperature in amber glass bottles, samples of each of the four formulations were subjected to hardness testing and disintegration determination. The storage data are presented in Table V. Statistical computation of the difference between the initial hardness and disintegration data means presented in Table III and the storage data means revealed no statistically significant changes in these parameters.

The Student *t* test (Eq. 1) was calculated for each

$$tn1 + n2 - 2 = \frac{\bar{X}_1 - \bar{X}_2}{Sp\sqrt{1/n_1 + 1/n_2}} \quad \text{(Eq. 1)}$$

of the four formulations, at 28 degrees of freedom for the hardness data, and at 10 degrees of freedom for the disintegration data, at the p 0.05 significance level. The initial mean values of Table III are identified as $\bar{X}_1$, and the storage data means as $\bar{X}_2$. The Sp standard deviation values were computed using Eq. 2, in which S_1^2 is the estimated variance of the initial Table III data, and S_2^2 is the estimated variance of the Table V storage data.

TABLE V—FOUR MONTHS' STORAGE DATA

Formula	Hardness,[a] Kg.	Disintegration,[b] min.
(*a*)	4.9	7
(*b*)	6.0	8
(*c*)	5.9	11
(*d*)	5.7	12

[a] Means of 15 tablets. [b] Means of 6 tablets.

$$Sp = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}} \quad \text{(Eq. 2)}$$

For the hardness data, the tabled critical t value is 2.048. For the disintegration data, the tabled critical t value is 2.228. Computation of t values for the hardness data for the four formulations: (*a*) 2.02, (*b*) 2.03, (*c*) 1.95, (*d*) 2.03. Computation of t values for the disintegration data: (*a*) 2.17, (*b*) 2.04, (*c*) 1.99, (*d*) 1.97. The hypotheses that there are no differences between initial and storage data sets of means are accepted.

SUMMARY

Using a chewable multivitamin tablet formulation containing dry malt solids as the binder, a series of isopropanol–water granulating solutions was evaluated along with water alone and isopropanol alone.

It was found that the higher the ratio of water content in the granulating solution, the lesser the percentage of residual fines that passed through a 60-mesh screen. However, the percentage of granules that were 30-mesh or larger was not significantly influenced by the higher water content. It was found that the presence of some water content was necessary with this formulation to achieve a suitable granulation. The isopropanol alone granulating solution was unsatisfactory for use.

The tablets prepared were evaluated in terms of the physical parameters: weight, hardness, thickness, disintegration, and friability. No difference was noted in the tablet friability of the four compressed granulations. The thickness obtained appeared to be dependent on the percentage of residual fines in the granulations, maintaining the weight and hardness of compression as constants. There was an unexplained lengthening in the initial disintegration of the tablets prepared with the higher isopropanol content granulating solutions.

Evaluation of the 4 month's storage samples revealed no statistically significant changes occurring in the hardnesses and disintegrations of the four tablet formulations.

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